ORIGINAL ARTICLE

Assessment of Relationship of Coronary Artery Disease Severity and 30 Days Outcome in Patients with Non-ST Elevation Myocardial Infarction with ST Segment Elevation and T Wave Change in Lead aVR

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ABSTRACT

Objectives: ST elevation in lead aVR (STEaVR) is considered to be a predictor of left main/ or triple vessel coronary artery disease (CAD) in patients with Non- ST Elevation Myocardial Infarction (NSTEMI). STEaVR and positive T wave in aVR have been shown to be related with increased mortality in patients with NSTEMI. The aim of this study was to investigate the association of STE aVR and ratio between ST segment in aVR and T wave amplitude in aVR (STaVR/TAaVR) with left main/triple vessel disease (LM/TVD), Syntax Score (SS) and 30 days major adverse cardiac events (MACE).

Methods: 402 consecutive NSTEMI patients undergoing coronary angiography were included in this prospective observational study. Patients were divided into two groups, based on ST segment elevation (defined as ⩾0.5mm) in lead aVR. The ratio using absolute values of STaVR and TAaVR were calculated- Ratio 1: STaVR/TAaVR and Ratio 2: TAaVR/STaVR. Syntax score was calculated using Coronary angiography (CAG) images. Study variables were compared between two groups.

Results: NSTEMI patients with STEaVR had higher rates of LM/TVD (39.5% vs 26%, p=0.011), and higher value of SS (17.8 vs 14.4, P=0.001). A significant positive correlation was observed between SS and STEaVR (r=0.21, P=0.001), SS and TAaVR (r=0.36, p=0.001), SS and ratio 1 (STaVR/TAaVR) (r=0.28, p=0.001) as well as ratio 1 and MACE (r=0.23, p=0.001).

Conclusions: NSTEMI patients with ST elevation in aVR have significantly higher rate of LM/TVD. STEaVR and positive T wave in aVR correlates with Syntax Score. The ratio (STaVR/TAaVR) may be useful to predict severity of CAD in NSTEMI.

Keywords: Coronary artery disease; lead aVR; major adverse cardiovascular events; non ST elevation myocardial infarction; Syntax score

INTRODUCTION

Cardiovascular diseases are a major cause of morbidity as well as frequent hospitalizations and account for nearly one-third of all the deaths[1]. Non-ST elevation acute coronary syndromes (NSTE-ACS), comprises upto 60-70% of ACS patients having varying degrees of atherosclerosis. The prognosis of these patients tends to vary as most of them are managed conservatively followed up with cardiac enzymes without early invasive intervention in absence of chest pain[2-4]. Non-specific electrocardiogram (ECG) findings such as ST segment depression, negative T waves in the precordial leads, ST segment elevation in lead aVR (STEaVR) and positive T waves in lead aVR are detected in approximately 60-70% of NSTE-ACS patients. These ECG changes are often shown to have a correlation with the severity of coronary artery disease (CAD)[5,6]. Multiple studies have revealed that STEaVR predicted left main involvement or (LM/TVD) in NSTE ACS[7,8]. Several studies have shown an increased mortality in NSTE-ACS patients with STEaVR as compared to those without ST elevation in

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aVR[9,10], however, this finding has not been confirmed in all studies[11].

The Synergy between percutaneous coronary intervention (PCI) with Taxus and CABG (SYNTAX) Score (SS) is a comprehensive scoring method used to show the severity of CAD and predicting short term and long term prognosis in NSTEMI[12]. Few studies have found an association between mortality and T wave amplitude in lead aVR (TAaVR) in the patients with STEMI and NSTEMI[13,14]. Although it has been found that positive TAaVR and elevated STaVR affect the prognosis adversely in patients with NSTEMI, there is no concluding study evaluating their role in assessment of CAD severity[15]. In addition, the role of a positive T wave for determining the extent of coronary stenosis is not well known. Early identification of patients with severe CAD is an important factor in the prognosis and selection of the optimal treatment strategy in patients with NSTEMI as high risk may benefit from early invasive therapies like (PCI) or coronary artery bypass graft (CABG). Specific ECG findings may be useful when added to risk score systems which predict prognosis such as GRACE (Global Registry of Acute Coronary Events) and TIMI (Thrombolysis in Myocardial Ischemia), and predict the severity of CAD disease in NSTEMI[16,17].

Previously described scores predict poor prognosis but not necessarily correlated with LM/TVD. Regarding these facts, we investigated the role of ST segment elevation in aVR (STEaVR) or ratio between ST segment in aVR and T wave amplitude in aVR (STaVR/TAaVR) with CAD severity by observing their association with left main(LM)/ or triple vessel coronary artery disease and SYNTAX Score. This study also aimed to find an association between STEaVR and STaVR/TAaVR ratio with one-month major adverse cardiac events (MACE) defined as death, recurrent myocardial infarction, stroke, major bleeding and target vessel revascularization.

MATERIALS AND METHOD

Study design and patient population: This was a single centre, prospective observational study performed at the Department of Cardiology at a tertiary care medical center from April 2018 to Jan 2020. The study complied with the ethical principles stated in the Declaration of Helsinki and was approved by institutional ethical committee. Written informed consent was obtained from each participant. A total of 402 consecutive patients (age >18 years) with recently diagnosed NSTEMI and undergoing coronary angiogram were included. A diagnosis of NSTEMI was based on presence of symptoms suggestive of acute coronary syndrome along with an elevated cardiac troponin-T exceeding the 99th percentile of normal reference limit without ST segment elevation[18]. Patients having an ECG finding on presentation indicative of STEMI, with pre existing ECG abnormalities affecting ST-T changes such as left or right bundle branch block, left ventricular hypertrophy, ventricular pacing, ventricular pre-excitation, non-ischemic cardiomyopathy, acute pulmonary embolism, severe valvular heart disease and aortic dissection were excluded. Patients who had recent (<6 months) PCI or prior CABG, severe renal function disorders (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2), hepatic function disorder or having a clear alternate cause for the symptoms, active or chronic inflammatory conditions were excluded.

Study procedures and laboratory analysis: Demographic characteristics, medical history, presenting symptoms, CAD risk factors, physical examination, duration of pre-hospital delay, biochemical and ECG findings, hospital stay and 30 day outcome data were collected. Cardiac biomarkers including cardiac Troponin-T was analysed using radiometer AQT90 flex analyzer and serum Creatine Kinase Myocardial Band isoenzyme (CK-MB) was measured using autoanalyzer. Renal function test, lipid profile, complete blood count, differential leucocyte count, platelet count were obtained using standard biochemical techniques using separate autoanalyzer.

A 12-lead surface ECG (rate 25 mm/s, standard 1mV/10mm) was recorded within 10 minutes of presentation in emergency, or whenever patient deteriorated clinically or complained of chest pain. At least three ECGs were obtained during the period of hospitalization. ST segment elevation was defined as ST segment elevation $\geqslant$ 0.05 mV (0.5mm) in the limb leads and ST segment elevation $\geqslant$ 0.1 mV (1mm) in the precordial leads using the preceding TP segment as a baseline. T wave amplitude in aVR (TAaVR) was measured depending on the PR segment in lead aVR. Negative and positive numeric values according to below or above location of ST segment or T wave in lead aVR were recorded using digital caliper. The absolute values of

STaVR and TAaVR were obtained and the following ratios were calculated- ratio 1: STaVR/TAaVR and ratio 2: TAaVR/STaVR.

Coronary angiography (CAG) was performed through femoral or radial artery access (Judkin's technique), using manual injection of low osmolar, non-ionic contrast (Iohexol) by treating physician after obtaining a written informed consent. Stenosis diameter ⩾ 70% with quantitative angiography was accepted as significant. The Syntax score (SS) was calculated by including the vessels with a diameter larger than 1.5mm and a stenosis over 50% from CAG images. All patients received aspirin, clopidogrel or tecagrelor, heparin or enoxaparin, beta blocker, angiotensin convertase enzyme (ACE) inhibitor according to the disease profile as per treatment guidelines for NSTEMI[19,20]. After one month of the index event, data regarding major adverse cardiac events (MACE) were obtained during outpatient clinic visit or telephonically, which were defined as a composite of all-cause mortality, cardiac death, stroke, non-fatal MI, target vessel revascularization (TVR), major bleeding according to the Academic Research Consortium definition[21]. Cardiac death was defined as death resulting from any cardiac-related causes. Non-fatal myocardial reinfarction was defined as increased cardiac biomarkers, characteristic dynamic and evolving electrocardiographic changes and prolonged chest discomfort), or emergency PCI. TLR was defined as repeat revascularization caused by ⩾ 50% stenosis within the stent or within 5 mm proximal or distal to the stent. Major bleeding was defined as bleeding requiring transfusion or surgery, decrease in hemoglobin of ⩾5 g/dl, and intracranial hemorrhage.

Statistical analysis: The study participants were divided into two groups based on presence of ST elevation in aVR: Group 1 including NSTEMI patients with ST elevation in Lead aVR and group 2 including NSTEMI patients without ST elevation in aVR. The study variables were divided as categorical and continuous variables. The Continuous data were expressed in mean and standard deviation and unpaired 't' test was applied to compare the variables. The categorical data were expressed in numbers, proportion and percentages, and chi square test or Fisher exact test was applied to compare. Pearson correlation coefficients were used find out correlation between Syntax score and various variables. Linear regression analysis was done for major cardiac indices and regression line with R^2 was found. ROC curve was drawn between true positive rate (Sensitivity) and false positive rate (1-Specificity) of LM/TVD to find out the Area under Curve (AUC). The statistical analyses were performed using the SPSS 24.0 (SPSS Inc., Chicago, IL) software in windows operating system. p value <0.05 was considered significant.

RESULTS

A total number of 402 patients were included in this study. The mean age was 56.38±9.53 years, ranging from 31 to 76 years and 59.2% of the patients were males. Demographic data of the two groups are presented in Table 1. A total of 119 patients (29.6%) had ST elevation in aVR ⩾ 0.5 mm while 78 patients (19.4%) had positive T wave in aVR.

Patient characteristics: In the study groups, no significant differences were found regarding the age, history of smoking, diabetic status, time of onset of ischemic symptoms, hemoglobin, high-density lipoprotein (HDL) and triglyceride levels. Patients in group 1 had statistically significant higher BMI levels, higher systolic and diastolic blood pressure levels, higher levels of creatinine, total cholesterol and low density lipoprotein (LDL). Group 1 patients also had significantly higher levels of Troponin-T and CK-MB. Patients with ST elevation in aVR had significantly lower levels of LV ejection fraction.

Coronary angiographic findings and cardiac procedures during hospitalization

Coronary angiography was performed in all recruited patients. Coronary angiographic data, depicted in table 2, revealed that almost half of the patients (44.8%) had single-artery disease, which did not differ between the two groups. However, Group1 patients had significantly higher rate of LAD involvement (68.9% vs 59%; p=0.001) as well as higher proportion of LM/TVD as compared to Group 2 (39.5% vs 26%; p=0.011). While plotting receiver operator curve (ROC) for STEaVR ⩾ 0.5 mm, the sensitivity for LM/TVD came out to be 28.9% and specificity came out to be 83.9% (Figure1). Also, patients in Group 1 had significantly higher mean Syntax score (SS) as compared to those in Group 2 (17.8 vs 14.4; p<0.001). In our study, there was no difference in the number of patients undergoing PCI or CABG between the two groups. In the correlation analysis, a statistically significant positive correlation was observed between ST

elevation in lead aVR and SS (r=0.21, p=0.001) (Figure 2), T wave in aVR with SS (r=0.36, p=0.001) as well as Ratio1 (STaVR/TAaVR) and SS (r=0.28, P=0.001) (Figure 3).

Predictors of 30 day outcome: Total number of patients who could be followed up was 368. A total of 67 patients (16.6%) patients had major adverse cardiovascular events (MACE) at one month follow up. There was a trend towards higher rate of MACE in Group 1, however the differences did not reach a statistical significance. We observed a statistically significant positive correlation between MACE and SS (r=0.32, P=0.001), as well as MACE and ratio 1 (r=0.23, P=0.001).

DISCUSSION

The present study showed that 29.6% of patients with NSTEMI had ST-segment elevation in lead aVR. The main finding of our study is the significant association of ST elevation in lead aVR as well as ratio 1 (STaVR/TAaVR) with CAD severity determined by left main/ triple vessel disease (LM/TVD) and syntax score on coronary angiography. In addition, this is the first study in Indian population to report that the NSTEMI patients with ST elevation in lead aVR had higher rates of LM/TVD and Left anterior descending (LAD) artery involvement. The possible mechanisms of such associations may be transmural ischemia of the basal interventricular septum or circumferential subendocardial ischemia of the left ventricle owing to significant disease in left main coronary artery or proximal left anterior descending artery. In such case, the ST-segment vector in the frontal plane points in a superior direction leading to ST-segment elevation in lead aVR[22-24].

The higher prevalence of ST-segment elevation in aVR (29.6%) observed in our study was comparable to that reported in prior studies (26-32.3%)[8,10]. Our study found a significantly higher rate of LM/TVD in patients with STEaVR as compared to patients without STEaVR (39.5% vs 26%, p=0.011). Misumida et al., previously in a retrospective analysis of 379 NSTE-ACS patients, reported that subjects with ST elevation in aVR had a significantly higher rate of LM/ triple vessel disease than those without STEaVR (39% vs 18%, respectively, p <0.001)[8]. In an another retrospective analysis of 1042 patients with NSTE-ACS, Barrabés et al., documented that patients having ST elevation in lead aVR had a higher prevalence of LM/ triple vessel disease with an increased mortality as compared to patients without STE in aVR[10]. In addition, Kosuge et al. showed that NSTE-ACS (n=333) patients with ST elevation (>0.05 mV) in aVR had an increased risk of LM/ TVD and death or reinfarction at 90 days[25]. Similarly, Szymanski et al. demonstrated that all cause mortality within 30 days was higher among the patients with ST elevation in aVR and is based on its relationship with multivessel disease and left main coronary artery obstruction[26]. We found that NSTEMI patients with STEaVR ⩾ 0.5mm had higher proportion of MACE at 30 day, however it did not achieve statistical significance. Yan et al. also observed that ST elevation in lead aVR ⩾ 1 mV was not an independent predictor of in-hospital and 6-month mortality after adjustment by GRACE risk score[11]. Thus, in agreement with previous studies, our study confirmed the role of STEaVR in predicting LM/TVD in NSTEMI patients with a lower sensitivity of 28.9% but a good specificity of 83.9%, as compared to prior study, where STEaVR identified LM/TVD with a sensitivity of 78% and specificity of 86%[25].

Syntax score is widely used in the evaluation of angiographic severity and extent of coronary lesions, and has been shown to predict mortality in addition to its role in the decision-making process of interventional procedure[27]. In our study, we observed that patients with STEaVR had significantly higher value of SS (17.8±9.8 vs 14.4±8.9, p=0.001) as compared to those without STEaVR. We also found a significant positive correlation between STEaVR and SS (r=0.21, p=0.001).

Our study also observed a statistically significant correlation of T wave amplitude in aVR with Syntax score (r=0.36, p=0.001). However, we did not observe any correlation between T wave amplitude and 30 day MACE. T wave which represents the repolarization of ventricles can be inverted due to disruption of normal physiologic repolarization of cardiac myocytes. Inversion of T wave in lead aVR manifests as a positive T wave[28]. Separham et al. demonstrated that positive T wave in lead aVR was an independent predictor of LM/ TVD however; it was not an independent predictor of MACE in patients with NSTEMI[14]. In a recent study, Icen et al. determined the amplitude of T wave and ST segment deviation in lead aVR 306 patients with NSTEMI and calculated a ratio by

dividing the variable with larger absolute value by other variable with a smaller absolute value in lead aVR. They showed that this ratio was strongly and independently associated with Syntax Score[15]. We analyzed a proportional combination of absolute values of STaVR and TAaVR ratio as a whole and found a significant association of ratio 1 (STaVR/ TAaVR) with SS (r=0.28, p=0.001) as well as MACE (r=0.23, p=0.001).

The strengths of our study were that this was a prospective study including 402 patients of NSTEMI with a one month follow up to observe MACE. We excluded patients with posterior (inferolateral) wall MI presenting with ST-segment depression in V1–V4, which is equivalent of STEMI. Serial ECGs were done to properly evaluate the patients with NSTEMI. Limitations of our study included that it was single center study with a relatively small sample size and a limited duration of follow-up. Multicentered and controlled studies with large sample size and long term follow up, are needed to support the strong correlation and independent determination of these ECG variables.

CONCLUSION

ST segment elevation in lead aVR on surface ECG which is a non-invasive, simple, economical tool may predict Left Main/ triple vessel diseases in NSTEMI patients. ST elevation in aVR and positive T wave in aVR correlates well with syntax score which is a marker of coronary artery disease severity. The ratio (STaVR/TAaVR) may be more useful to predict severity of CAD and short term MACE in patients with NSTEMI, if added to risk scoring methods and rapid decisions for early intervention and revascularization could be taken in such patients.

Table 1: Comparison of demographic, clinical and laboratory findings of study participants between the two groups

	NSTEMI patients with ST Elevation in aVR (STEaVR) GROUP 1(N=119)	NSTEMI patients without ST Elevation in aVR (STEaVR) GROUP 2 (N=283)	p Value
Age (years)	56.7±8.9	56.3±9.8	0.7(NS)
Males	73 (61.3%)	165 (58.3%)	0.32 (NS)
Females	46 (38.7%)	118 (41.7%)	0.32 (NS)
BMI (kg/m2)	24.7± 4.8	23.8± 5.4	**0.003(S)**
Smoker	38 (31.9%)	104 (36.7%)	0.14 (NS)
Hypertension	57 (47.8%)	87 (30.7%)	**0.002(S)**
Diabetes	50 (42%)	101 (35.6%)	0.27 (NS)
Dyslipidemia	47 (39.4%)	79 (27.9%)	**0.03 (S)**
Family history	36 (30.2%)	80 (28.2%)	0.79 (NS)
H/O CAD	24 (20.1%)	38 (13.4%)	0.11 (NS)
Time of onset(hours)	9.39± 5.25	9.12± 4.8	0.22 (NS)
Troponin- T(ug/L)	0.23±0.24	0.15±0.28	**<0.001 (S)**
CK-MB(IU/L)	66.07±16.02	53.08±10.6	**<0.001 (S)**

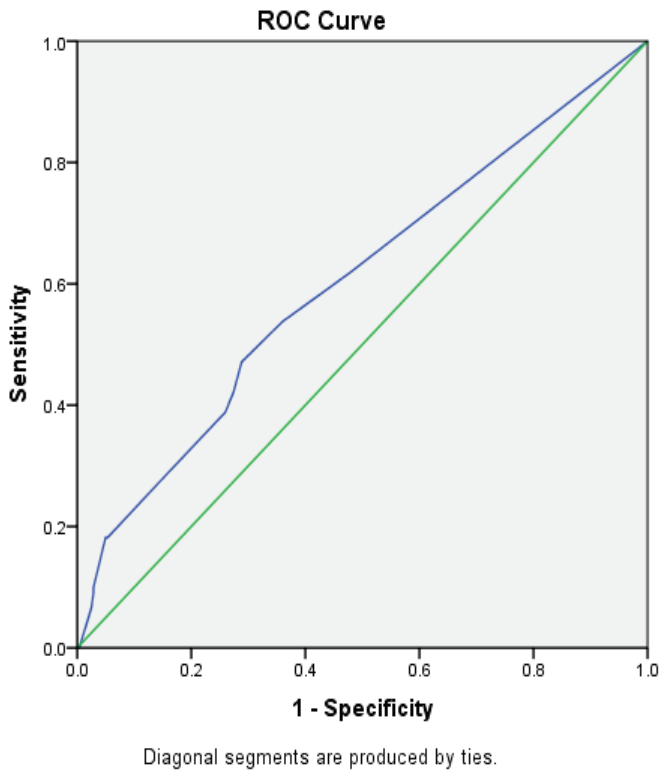
	NSTEMI patients with ST Elevation in aVR (STEaVR) GROUP 1(N=119)	NSTEMI patients without ST Elevation in aVR (STEaVR) GROUP 2 (N=283)	p Value
SBP (mm of Hg)	138.4±21.8	132.5±20.4	**0.009 (S)**
DBP (mm of Hg)	85.3±12.3	81.4±11	**0.002 (S)**
Creatinine (mg/dl)	1.19±0.3	1.1±0.3	**0.006(S)**
Total Cholesterol (mg/dl)	182.9±41.9	173.6±36.6	**0.027 (S)**
LDL (mg/dl)	112.1±36.7	103.9±36.9	**0.042 (S)**
LVEF (%)	52.98±6.08	54.4±5.7	**0.026(S)**
RATIO1 : STaVR / TAaVR	0.35±0.23	0.04±0.12	**<0.001 (S)**
RATIO 2 : TAaVR/STaVR	3.46±2.07	7.57±13	**<0.001 (S)**

BMI= Body mas index, CAD= coronary artery disease, CK-MB= Creatine Kinase Myocardial Band isoenzyme, DBP= Diastolic blood pressure, HDL= High density lipoprotein, LDL= Low density lipoprotein LVEF= left ventricular ejection fraction, NSTEMI= Non ST elevation myocardial infarction, SBP= Systolic blood pressure, STaVR= ST segment change in lead aVR, TAaVR= T wave amplitude in lead aVR.

Table 2: Comparison of coronary angiography findings and outcome of study participants between the two groups

	NSTEMI patients with ST Elevation in aVR GROUP 1(N=119)	NSTEMI patients without ST Elevation in aVR GROUP 2 (N=283)	p VALUE
SVD	46 (38.6%)	134 (47.3%)	0.12 (NS)
DVD	36 (30.2%)	63 (22.2%)	0.09 (NS)
LM /LM+TVD	47 (39.5%)	74 (26%)	**0.011 (S)**
Insignificant CAD	14 (11.7%)	33 (11.7%)	0.9 (NS)
LAD	82 (68.9%)	167 (59%)	**<0.001 (S)**
LCX	57 (47.8%)	121 (42.7%)	0.40
RCA	50 (42%)	128 (45.2%)	0.63
LM	42 (35.2%)	52 (18.3%)	**<0.001 (S)**
Syntax score (SS)	17.79±9.78	14.43±8.9	**<0.001 (S)**
PCI	63 (52.9%)	181 (63.9%)	0.06 (NS)
CABG	17 (14.2%)	28 (9.9%)	0.27 (NS)
MACE	24 (20.2%)	43 (15.2%)	0.28 (NS)

CAD= coronary artery disease, CABG= coronary artery bypass graft, DVD = double vessel disease, LAD=Left anterior descending, LCX= left circumflex, LM= left main, MACE= major adverse cardiovascular events, PCI= percutaneous coronary intervention, RCA= Right coronary artery, SVD= single vessel disease, TVD= Triple vessel disease.



	STEaVR ⩾5mm
Sensitivity	28.9%
Specificity	83.9%
AUC	0.602
95% CI	0.54-0.66

Figure 1: ROC curve for ST elevation in aVR for predition of Left main/Triple vessel disease on coronary angiography.

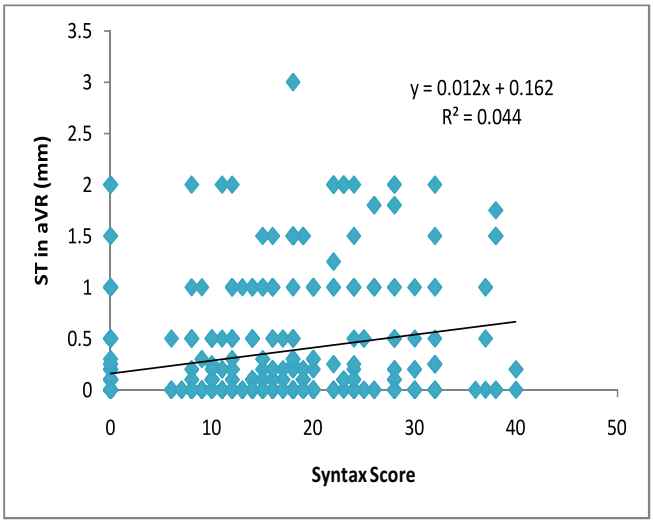


Figure 2: Correlation of Syntax score with ST elevation in lead aVR.

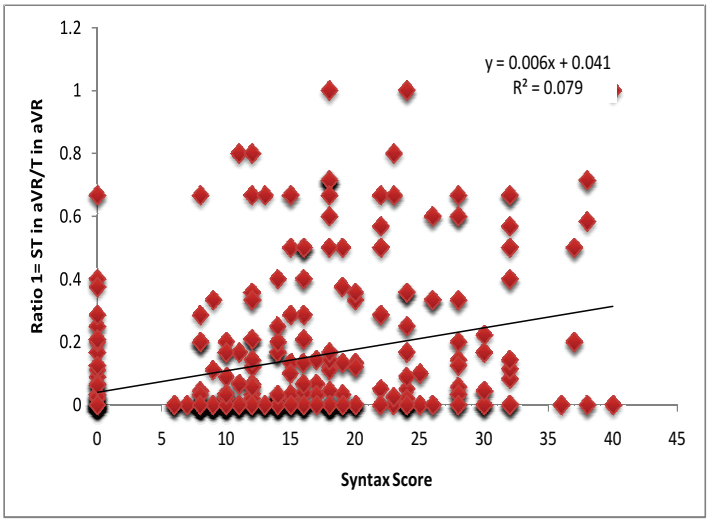


Figure 3: Correlation of Syntax score with ratio 1 (STaVR/TAaVR).

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